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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/701,236	11/04/2003	Stanley T. Crooke	ISIS-5207	5280

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WOODCOCK WASHBURN LLP
CIRA CENTRE, 12TH FLOOR
2929 ARCH STREET
PHILADELPHIA, PA 19104-2891

EXAMINER	
CHONG, KIMBERLY	
ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
03/16/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

eofficemonitor@woodcock.com

Office Action Summary	Application No.	Applicant(s)	
	10/701,236	CROOKE, STANLEY T.	
	Examiner	Art Unit	
	KIMBERLY CHONG	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 December 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,71-73 and 76-79* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,71-73 and 76-79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response has been considered. Rejections and/or objections not reiterated from the previous office action are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 71-73 and 76-79 are pending in the application.

Claim Rejections - 35 USC § 103

The rejection of claims 1, 71-73 and 76-79 under 35 U.S.C. 103(a) as being unpatentable over Wyatt et al. (Nucleic Acids Research 1989, vol. 17, pages 7833-7842), Monia et al. (Journal of Biological Chemistry 1993, vol. 268, pages 14514-14522), Manche et al. (Molecular and Cellular Biology 1992, of record) and Baracchini et al. (US 5,801,154, of record) is maintained for the reasons of record.

Response to Arguments

Applicants argue no reason has been provided why one of skill in the art would have made the claimed compounds prior to invention by the applicants. Applicants argue the Wyatt article does not describe or suggest fully complementary oligomeric compounds consisting of 17 to 25 linked nucleosides in which each strand of the duplex comprises at least one modified nucleoside that comprises a sugar surrogate.

Applicants argue the other references fail to suggest such modification in both strands. Applicants argue a previous declaration described that both Manche and Baracchini fail to provide such a teaching or suggestion because Manche describes unmodified duplexes and Baracchini is directed to single stranded oligonucleotides.

With regard to Monia applicants argue this reference does not suggest incorporation of a least one modified nucleoside that comprises a sugar surrogate into both strands. Applicants state that Monia utilized duplexes in which only one strand contained modifications and further state that in the experiments in which the antisense activity of the single-stranded gapmers was analyzed the duplexes were not introduced into HeLa cells, but instead single-stranded gapmers were introduced and their activity against unmodified, full-length mRNA target was determined.

Applicants argue there would have been no reason to incorporate chemical modifications into both strands of a duplex because the experiments described in the cited references do not involve conditions in which undesired nucleolytic degradation of such duplexes could have occurred. Applicants state the *in vitro* experiments described in the references use only one endonuclease where no other enzymes were present and the experiments in which nucleic acids were introduced into cells or were treated with cellular extracts used single- stranded oligonucleotides targeted against full-length mRNAs; double-stranded duplexes were not utilized.

Applicants' arguments have been fully considered but are not persuasive. With regard to the Wyatt reference, it is correct that this reference does not teach a duplex in which each strand comprises at least a sugars surrogate, but it was not relied upon for

such a teaching. Similarly, no one reference cited teaches all the limitations of the instant claims, however such a teaching is not required because the claims have been rejected for obviousness, not anticipation.

As stated in the rejection, the reason to produce a duplex with modifications in each strand comes from the teachings in Monia that nucleolytic degradation is a problem for nucleic acids and that stabilization of a duplex with modified nucleotides such as 2'-Omethyl provide resistance to nucleases. Even in the absence of an explicit exemplification of such a duplex the person of ordinary skill in the art would recognize that the duplexes taught by the references would be susceptible to nuclease degradation if placed into a cellular environment and would recognize that this problem could be corrected by inclusion of a modification in both strands. Applicants assert such a solution is unnecessary because none of the cited references use a duplex in such conditions, but this assertion is incorrect.

Applicants state that experiments described by Monia only used only single-stranded gapmers combined with unmodified, full-length mRNA target and no duplexes were introduced into HeLa cells. However, as noted in the rejection Monia does in fact use short duplex RNAs in cell extract experiments. Monia states at page 14517, column 2 that the ability to direct RNase H cleavage of a complementary RNA by 2"O-methyl deoxy gap oligonucleotides was determined *in vitro* using HeLa nuclear extracts and refers to figure 4. The legend for figure 4 states, "a synthetic, end-labeled, 25-mer RNA containing mutant Ha-ras codon 12 sequences...was preannealed with the appropriate oligonucleotide and treated with HeLa RNase H for 10 min at 37 °C. Following

termination of reactions, cleavage products were resolved on a 20% acrylamide gel under denaturing conditions. A, 2 µg of HeLa extract added; B, 0.2 µg of HeLa extract added."

Based on the teachings of the cited reference the person of ordinary skill in the art would recognize that short duplexes were routinely used for the purpose of studying the activity and structural requirements of different enzymes, that these duplexes could be and were used under conditions where they might be susceptible to nuclease cleavage, and that one way to reduce this susceptibility was to include modified nucleotides such as a sugar surrogate. Therefore the claimed invention would have been obvious to the person of ordinary skill in the art at the time the invention was made.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Thursday between 6 and 3 pm.

If attempts to reach the examiner by telephone are unsuccessful please contact the SPE for 1635 Heather Calamita at 571-272-2876. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Kimberly Chong/
Primary Examiner
Art Unit 1635